PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/004371	26.04.2004	30.04.2003

International Patent Classification (IPC) or both national classification and IPC
A61P9/00, A61K31/5386, A61K31/547, C07D513/08, C07D498/08

Applicant
ACTELION PHARMACEUTICALS LTD

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 8-10

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 8-10

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 8-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.

Reference is made to the following documents:

D1: WO 97/09311 A (HOFFMANN LA ROCHE) 13 March 1997

D2: US-A-3 509 161 (DOLD OTTO ET AL) 28 April 1970

D3: CHEN, ZHENGMING ET AL, JOURNAL OF MEDICINAL CHEMISTRY , 39(24), 4744-4749, 1996, XP002291893

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e the 6,7-disubstituted 9-azabicyclo[3.3.1]non-6-ene of formula (I) according to claim 1, appears to fulfil the requirements of novelty, cf. Article 33(2) PCT:

The compounds of D1-D3 differ form those presently claimed because instead of the 9-azabicyclo[3.3.1]non-6-ene ring with a heteroatom in the 3-position, they have:
- a piperidine or 8-azabicyclo[3.2.1]octane ring in D1;
- a 9-azabicyclo[3.3.1]non-2-ene or 8-azabicyclo[3.2.1]oct-2-ene ring in D2;
- 9-azabicyclo[3.3.1]nonene ring in D3 (see compound 9 in scheme 1).

2.

The current application is related to 6,7-disubstituted 9-azabicyclo[3.3.1]non-6-ene compounds that are renin inhibitors useful in the treatment of cardiovascular and renal diseases and hypertension.
Document D1, which is considered to represent the most relevant state of the art, discloses also renin inhibitors.
In D3, it is stated that the 9-azabicyclo[3.3.1]**nonane** compounds are known to possess hypotensive activity and in D2 it is shown that the 9-azabicyclo[3.3.1]non-**2**-ene or 8-

azabicyclo[3.2.1]**oct-2-ene** compounds are useful in the treatment of hypotension.

Due to the structural differences re the active compounds in D1 (the exchange of the piperidine or 8-aza-bicyclo[3.2.1]octane ring in D1 by a 9-azabicyclo[3.3.1]non-6-ene ring which is specifically substituted with a heteroatom in the 3-position) it cannot be said with any degree of accuracy that the skilled person, faced with the problem of providing further novel compounds with renin inhibitory activity, would have been unambiguously led to prepare the compounds of the present application- even by combination of D1 with D2 or D3.
For the purpose of assessing the inventive step during the International Preliminary Examination it is assumed that the claimed compounds do indeed possess the alleged activity. Thus and in absence of any more pertinent prior art, the present invention appears to involve an inventive step (Art.33(3) PCT), based on the renin inhibitory activity of the claimed compounds.

3.
For the assessment of the present claims 8-10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO03/093267 A1	13.11.2003	08.04.2003	29.04.2002
WO 2004/002957	08.01.2004	29.04.2003	27.06.2002

These documents are related to 4,3-disubstituted 1,2,5,6-tetrahydropyridines and to 7-aryl-3,9-diazabicyclo[3.3.1]non-6-ene derivatives as renin inhibitors.